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FINAL REPORT - CONTRACT NASW 1815
TO DEVELOP A SPECTRAL ANALYZER FOR PHYSIOLOGICAL AND MEDICAL USE

**CASE FILE
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To
Office of Life Sciences
Bio Research Program
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INTRODUCTION

The purpose of this program (and its predecessor program, NASW-1066) has been to develop the scientific requirements for a spectral analyzer to be used for monitoring mammalian subjects. Spectral analysis in the biological context is taken to mean the use of dynamic or time dependent data as a measure of the operating status of a subject. Physicians have long used such data, for example, the pulse rate, respiration rate, etc. In this program it was proposed to study an expanded list of dynamic parameters, to include such slower acting cyclic processes as metabolic rate and body temperature, and blood constituents like glucose, oxygen, carbon dioxide, and lactic acid. Metabolic cycles have been found with periodicities in the range of minutes and hours; longer cycles in body weight (3 1/2 days and 60 days), indicative of metabolic processes, have also been found.

As the longer period cycles have been found, attempts have been made to determine the processes which generate them. This is the key to dynamic analyses; to use the periodicities as a guide to help expose the physiological mechanisms. For example, the one second cycle heartbeat in humans has been highly important in elucidating operation and pathology in the underlying process.

As the program progressed it became apparent that the oscillating processes which were so ubiquitous represented the operation itself of living systems. It became apparent that all bioregulation was affected by mediation of these oscillating processes, that homeostasis (the guiding principle of bioregulation) was dynamic and accordingly we proposed the term homeokinesis to indicate that the bioregulation was really a function of time dependent processes.

A group was formed to study the systems dynamics. The group contained

consultants with expertise in anatomy, gross physiology, pharmacology, and neurophysiology, as well as the physical-chemical-electronic-biological expertise of GTS. The objective of the group activities was to develop a systems science for biology with emphasis on mammals, particularly man. It was felt that this approach was necessary to make the spectral analysis of biosystems meaningful and practical. At first, the group collaborated informally and some theoretical and experimental work and publications resulted. Added support from the Army Research Office has expanded the program. Joint meetings, discussions, and experimental collaboration has led to firmer interaction among the members.

One result of this collaboration is NASA Contractors Report CR-1720, entitled "Introduction to a Biological Systems Science". The authors are E. H. Bloch, Associate Professor of Anatomy, Case-Western Reserve Medical School; D. Jacobowitz, Assistant Professor of Pharmacology, University of Pennsylvania Medical School; K. Kornacker and L. Lipetz, Professors of Biophysics, Ohio State University; W. McCulloch (deceased), formerly Professor in Bioengineering, M.I.T.; J. Urquhart and F. Yates, Professors of Biophysics, University of Southern California; and A. Iberall, physicist, S. Cardon, chemist, and M. Weinberg, physiologist, General Technical Services, Inc. Our current group also includes D. Winter, neurophysiologist, formerly at Walter Reed Institute for Research, and P. Hollander, Professor at Ohio State Medical School.

Joint papers have been published by Iberall and McCulloch, and Cardon, Oestermeyer (Case-Western Reserve) and Bloch. Joint experiments are in process between Bloch's group and Hollander, and Bloch and GTS.

The program with this group of collaborators thus represents a real attempt at a directed interdisciplinary systems attack on biological problems.

This kind of approach has been frequently mentioned in recent years as a necessary requirement for solving these difficult and important problems. We are grateful to NASA and the Army Research Office for having made it possible for us to start such an effort.

As the dynamics or time dependent aspects are clarified, they will be applied to the Army medical problems of monitoring, diagnosis, and treatment.

WORK PERFORMED IN THIS PROGRAM

The reports and publications of this program (and its predecessor program, NASW-1066) are listed in the enclosed bibliography.

The program started with the paper by Iberall and Cardon on Control in Biological Systems (1). This paper was a survey of biological thinking with an attempt at critical assessment in terms of the control engineer. A major line was traced from Bernard to Cannon (homeostasis) to Weiner (cybernetics) and Homer Smith. It appeared clear that Cannon understood the engineering ideas of regulation and was interpreting mammalian regulation in these terms. It was pointed out that there was some confusion between regulatory phenomena and aperiodic alarm systems (hunger, thirst, etc.). A start was made to apply strict engineering concepts and a brief survey of oscillator phenomena was made. Earlier work by Iberall had disclosed dynamics in temperature regulation (heat production and metabolism) and the initial conclusion had been that regulation in these areas was dynamic. The oscillator phenomena studied in this paper showed such operations to be ubiquitous in living systems and the conclusion in later reports was that likely all bioregulation was dynamic. The program then took up the task of demonstrating oscillations and attempting to use them to help unravel physiological process mechanisms.

The original program was organized into four main sections, thermoregulation, hydrodynamics of the cardiovascular system, hormonal regulation, and behavior. Both theoretical and experimental work was done, especially regarding regulation of temperature and the concentration of blood constituents. Temperature surveys were made over the human body to demonstrate the dynamics, and followed up with animal experiments, to attempt to arrive at temperature

and metabolism balances. In general the following results have been obtained in the different areas.

1. Thermoregulation

The following model of mammalian thermoregulation has been developed. Mean metabolism is tied to activity level. It increases somewhat in cold or hot environment. However, this is a second order effect which will be ascribed to the extra energy charge put on the body for added working use of the blood. Metabolism therefore is a variable of temperature regulation; it is a follower basically of activity level.

The main process in thermoregulation appears to be the regulation of heat loss. In a warm environment the skin circulation is opened, increasing the skin blood flow and permitting increased evaporation and heat loss. In the cold, the skin circulation is cut off, thereby cutting down heat loss through the skin. A cut off skin temperature of approximately 30°C has been found, above which capillaries open and below which they close. This action was first observed in studies on surface temperatures in humans. It was subsequently also found in direct observations of the capillary beds in unanesthetized mice - in which a plastic window was placed over a muscle bed and the exposed tissue observed microscopically. An added factor is the fact that capillaries change their water permeability at about 35°C , thus greatly increasing the flow of water to the sweat glands. The action of the hypothalamus appears to be one of regularizing the flows of blood among the various organs and tissues. Thus, it is instrumental in regulating overall skin blood flow in different ambient temperature situations.

The model has been built up in part by consideration of the dynamics of temperature, metabolism, and blood constituents related to metabolism. Thus,

cycles with periodicities of 100 seconds, 400 seconds, 1200 seconds, and 3 1/2 hours have been seen in body and internal temperatures, ventilation and metabolic rates, and glucose, oxygen and carbon dioxide levels in the blood, and in the numbers of red cells per unit time flowing through capillaries. The adjustment to temperature changes of heat production and heat loss has been noted to be prominent at the seven minute level. This, and other evidence has suggested that the hypothalamus action to readjust blood flows may be a source of this cycle.

Our model has further considered the muscle tissues to be the major source of heat production - the resting muscles produce periodically coordinated heat power, with a fairly constant average level. The circulation through this core is well endowed, and since it is kept warm, near 37°C, the capillary beds are largely open. Their oxygen transport characteristics are dynamically regulated by some other signal (for which we have proposed an oxygen choke) to supply the power level required by muscles and organs for both the standby load, and any variable activity load that may be placed on the system. Peripheral circulations perform a self-regulatory function. At temperatures of 30°C and below they shut down. However, it is sensing at the hypothalamus that balances the subdivision of blood flow, as a zonal control.

As part of the experimental program, we have determined the rates of flow of red cells in capillaries in consideration of the fact that the red cells are the oxygen carriers. We have also determined the changing levels of oxygen, glucose, and carbon dioxide in the blood. The cyclic patterns have reflected the patterns of heat production and ventilation rate thereby showing the connections of metabolites and energy production.

2. Hydrodynamics of the Cardiovascular System

The modeling of the hydrodynamics of the cardiovascular system has followed from an earlier study (Iberall, National Bureau of Standards, 1950) on the transmission line characteristics of hydraulic lines. In addition to that work on attenuation of pressure, two others had modeled pressure-flow relations in arteries, Womersley (1957) at Wright Field and Witzig (1918) much earlier in Switzerland. In this program it was shown that all 3 results were in essential agreement, as far as arteries were concerned. Thus, arteries could be treated like hydraulic transmission lines. As far as the arterial pulse is concerned, the approximate characteristic of the CV system has been described as a 'windkessel' by Frank (1899). Thus, the basic nature of the arterial pulse seems to be a function of the microvasculatures resistive characteristics (which is fixed for any short period of time), and the elastic characteristics of the arterial tree. Applying a transmission model to the arterial system to account for the windkessel characteristics is difficult, in that in any artery there are many junctions with tributaries which produce reflections which cannot easily be treated mathematically. In this program, the problem was solved in two steps. First, the entire arterial tree was modeled geometrically, then the arterial tree was considered as equivalent to tapered tubes with branches represented by a 'porous' wall. The model of the arterial system is thus equivalent to a tapered porous tube. The geometric model of the arterial system has been adapted in a current biological handbook as a 'universal' arterial tree model. The dynamic transmission model has been a forerunner of and stimulus to a number of other efforts (Skalak and others).

More recent work has been concerned with regulation and control of

cardiovascular activities. For this purpose the cardiovascular system is considered as one demand subsystem of the metabolic system. The cardiovascular system serves a primary function of distributing oxygen, where the term 'primary' implies that the substance in blood, whose supply rate is a limiting factor for tissue metabolism, is oxygen. The many other substances convected by blood to tissue can be regarded collectively under three headings: fuel supply, water supply, and information flux. Of the cycles which have been found associated with metabolic activity (100 sec., 400 sec., 1200 sec., and three and 1/2 hours), the 400 second cycle has been considered the important one to consider for cardiovascular system analysis since a variety of cardiovascular mechanisms operating on this or shorter time scales interact to effect body-wide oxygen balance at an approximate 400 second level. At this time scale the regulation of cardiac output and of oxygen uptake are fundamentally connected.

An engineering view of the cardiovascular system has been attempted and this has been compared with the current biological views best represented by Guyton's work. Two such efforts have already been made. In the first, the Guytonian view has been examined and somewhat expanded. In the second, a broader background of physical design limitations have been brought forward to the system. Even though very recent, the arguments have been found provocative by some major CV researchers (e.g., M. Levy, Berne). The independent nature of pressure and flow control in the CV system has been stressed, and the physical requirements for physical modeling of these two regulatory systems has been proposed.

3. Hormonal Regulation

An initial approach to unravelling the complexities of hormonal behavior in line with the dynamic concepts proposed was to attempt the correlation of

particular hormones with particular periodicities. It was suggested that fast acting agents like the catecholamines would be more likely to affect rapid metabolic responses, whereas slower acting hormones like the steroids and thyroxine would more likely affect long time regulation. For example, we have left open the question of what regulates a 3 1/2 hour metabolic cycle. (At present, the most likely candidate seems to be cortisol); the 24 hour cycle (a link between melatonin and the catecholamines may be the 'Zeitgeber', but cortisol may support the daily cycle also); a 3 1/2 day water cycle (while aldosterone is a likely candidate, there is a much more remote possibility of a thyroxine cycle regulating both water and metabolism). The dynamic concepts would require that particular dynamic schemes or causal chains be identified over the appropriate metabolic paths.

A first model has been outlined on how the endocrine chains are linked together to produce the overall complex of metabolic responses. What is beginning to emerge from our work that a large part of the homeostatic 'control' in the body emerges more from chemical self-regulation, as a basic process, than so-called technical 'feedback'.

At the present point, we have taken the following stand. As noted in our latest contractors report: "Because of the multiplicity of loose couplings among metabolic chains, many indirect effects of hormonal action are possible and are observed. It is believed by many, for example, that an increase in the level of free fatty acids in blood decreases hepatic glycolysis and increases hepatic gluconeogenesis. If indeed, free fatty acids do control the operation of these two great metabolic chains in the liver, then an indirect effect on these chains may be expected from the actions of insulin, epinephrine, the sympathetic nervous system, growth hormone, thyroid hormone, glucocorticoids and even antidiuretic hormone, all of which affect the rate of secretion

of free fatty acids into blood from fat. The time domains in which the effects lie will depend upon the primary hormonal action, and the secondary action of free fatty acids on the hepatic processes. In such networks of coupled metabolic actions, a spectroscopic approach offers little hope of establishing causalities, as previously pointed out. What the spectroscopic approach can do is to identify periodic power fluxes, if they are present, and therefore to launch the quest for the informational flux initiating or sustaining the power flux. The information flux need not be periodic, even if the power flux is stabilized in a limit cycle mode". The emphasis has accordingly changed to an overall biospectroscopic approach to bioenergetics.

Experimentally, we have studied the oscillations in blood glucose levels, in the flow of red cells in capillaries, in blood oxygen, carbon dioxide and lactic acid levels. We have speculated on possible mechanisms for their mediation and have tentatively concluded that hormonal influences are likely most important.

The blood glucose has resulted in controversy with some denying the existence of oscillations. The problem has been discussed in several of our publications. It has been pointed out that one source of difficulty may be the use of automated analytical equipment which tend to damp out the oscillations. We have suggested that there is a general danger in indiscriminate use of such instruments in research, when these instruments have been developed for routine clinical laboratory use. Most often test instruments require careful modification for research purposes.

We have become involved in a number of such controversies, for example in addition to the question of significant blood sugar fluctuations, the issue of the existence and significance of precapillary sphincters, the

existence of fixed pores in the capillary wall, and quite a few others. We regard our role to be one of responsible critic and advocate of alternate views of bioregulation, - particularly dynamic - as it affects systems operation, and defer from or analysis of that operation. In this task we believe that we play a unique physical role, that is becoming more widely recognized as time goes on, in the biological field. This achievement has been made under our NASA - Army programs.

4. Behavioral Regulation

Initially, behavioral regulation was taken up as an independent regulatory function. However, it is now recognized that such action is simply an additional hierarchical level of system regulation. It has been suggested that behavior is modal with approximately twenty distinguishable 'action modes'. In accordance with the dynamic concepts, there are periodicities associated with these modes. Some modes are reactive to external stimuli, and some are endogenous. The concept of a body image and the primitive outline of a chemical basis for it has been proposed, based on the brain's knowledge of perhaps a half dozen compounds (e.g., serotonin, dopamine, etc.), which arise concomitant with metabolic activity. Thus, all non-reactive human behavior is both modal and periodic; the brain has a chemical basis for forming a body image of its structural and functional condition, and the body image is partially dependent upon modal constellations of hormones and metabolites in blood. These constellations, forming the body image are used by the reticular core and limbic system to urge decisions upon the cortex, and influence priorities among behavioral choices. (We have influenced such investigators as Kilmer, who has been modeling the reticular formations, and more recently hippocampal action.)

5. Regulation and Control

In addition to treating these four areas more or less independently, considerable effort has been expended on a generalized view of regulation and control in mammals. Our work on systems analysis in biology has been concerned primarily with the operations of the system, at the levels of organs, internal process organization and logic for the macrosystem. The first generalization developed from the realization that there is a ubiquity of biochemical oscillators in the biological system and that oscillatory processes are used for the essential regulation of the internal milieu of the system. That the system regulates internally to maintain its independence from the environment had been recognized by physiologists, notably Bernard, Sechenov, and Cannon. Cannon had coined the term 'homeostasis' to describe the regulatory activities of the complex animal, by which constancy is maintained in form and function (i.e., by reactive response to disturbances). There are limits beyond which blood pressure, body temperature, body composition, etc. do not go. As a result of the work on oscillating processes, we suggested that the term 'homeokinesis' would better describe the regulating processes, since it would indicate the dynamic character of those processes in contrast to the static regulation (or reactive nature) implied by Cannon's description.

To illustrate the ubiquity of oscillators in animals, one need only point to brain waves, heartbeat, respiration, menstrual cycles, and more recent findings of cycles in ventilation rate, metabolism, temperature, blood constituents (oxygen, carbon dioxide, glucose, lactic acid, free fatty acids, hormones - most recently cortisol), red cell flow in capillaries, water content, body weight, circadian rhythms, activity, and some behavioral states.

Many of the oscillators appear to be van der Pol relaxation oscillators. In fact we believe that the biooscillators are nonlinear limit cycles, ever-beating in the system. It is especially pertinent in biology that nonlinear oscillating systems can be shifted in operating point or show frequency entrainment either as synchronization or subharmonic resonance. This property makes it possible to change oscillator characteristics by small chemical or electrical triggers (e.g., catalytic signals) to the oscillator chains.

Examination of the variables being maintained constant (albeit by oscillating processes) showed that the constancy is not in a very narrow band as would be expected from precise regulators or controllers. It was concluded that the system operated mainly with fairly broad band regulators, essentially of a so-called 'bang-bang' (or a squirt system, or impulse system) nature. The overall regulation is adequate to maintain living systems viable for long periods of time. It has been suggested that the body has developed highly entrained primitive thermodynamic engine cycles for the basic self-regulation, and then built system of such regulation upon system. We have suggested that there were hierarchical levels of regulation, with each succeeding level producing a more responsive adjustment. In addition, each regulating level acted in a different time domain. An example is the blood pressure. The heartbeat acting in the one second time domain brings the arterial pressure close to the desired level. Beat to beat variation, operating in a slower time scale of 5 - 10 seconds, makes a correction dependent on a pressure measurement at the carotid sinus. A further correction is made by changes in the resistance in the microcirculation acting in the 100 second time domain.

A hierarchical system has similarly been structured for heat production.

Behavior, it has been suggested, also operates homeokinetically, by

oscillating processes. Mechanisms and time domains have been speculatively proposed for the various levels of activity in the central nervous system. Further, behavior represents additional levels of regulation, superimposed on the physiological levels of regulation affecting the same parameters generally in longer time periods.

Hierarchical regulation can be illustrated with regulation of water. Water is regulated in at least two processes in the minutes range, sweating at two minutes and seven minutes, a water cycle at the 60 - 90 minute range (McCally), water intake and urinary output in the circadian range, and a process at about three and a half days which is reflected in variations in overall body weight (females show sizable variations in body weight and water content in phase with the menstrual cycle); further there are seasonal cycles in body weight which are likely tied to water content.

Every regulation process requires a chain of elements whose individual times of action add up to the period of the overall chain thereby establishing the average period of the regulatory cycle. The system and its many chains are marginally unstable. It is this character that keeps the system and its internal fluxes in continued motion, always in the process of responding to changing inputs into the system (to the vicissitudes of the milieu, which appear as an impulsive spectrum).

6. Interdisciplinary Effort

The enclosed reports and publications provide in much greater detail the results achieved so far in this program. Of especial interest is the most recent NASA Contractors Report, which is a collaborative effort of ten investigators from six universities and General Technical Services. An attempt has been made to provide an introduction to a biological systems science by

putting forth a set of principles as a general systems science theoretic.

"They include the idea that a complex system is caught up in a large number of oscillatory chains - thermodynamic engine cycles - which maintain the average regulated states; that an autonomously operating system is marginally unstable so that it cannot come to rest; that such a system operates within many modes; that the autonomous system has to develop a complex behavior which is ordered in temporal and spatial scale via these modes".

"Various of the biological subsystems are discussed and analyzed in nearly unitary fashion, within the overall systems paradigm. The subsystems treated include the membrane, the microvasculature, the autonomic nervous system, the cardiovascular system, the biochemical chains, the higher nervous structure and function, and the hormonal foundations for behavior. The integration of behavior was intended, but not completed", due to Professor McCulloch's death when the report was in preparation. The report has been dedicated to his inspiring spirit.

The collaborative effort has led along several research paths. Doctors Bloch and Hollander have initiated experimental design study for the insertion of micro pipettes into microscopic vascular and extravascular elements. By direct observation of the microfield, using monochromatic light, optic and electronic image magnification, intensification and transmission equipment, the investigators are able to place micro pipettes into preselected tissue locations.

A series of experiments have evolved from this effort, from which ionic fluxes of sodium, potassium, calcium, hydrogen and chloride can be monitored across the capillary wall.

The investigators are seeking to find a correlation between the poten-

tials generated by one or more of these ions and the intermittancy of erythrocyte flow in the corresponding single capillary segment. Although the erythrocyte flow patterns have been widely observed, the heretofore accepted mechanism regulating this phenomenon, precapillary sphincter action, has lost much of its universal appeal. Most capillary beds have been shown to contain no active sphincteric mechanism. Yet these same beds have intermittent flow patterns.

The regulatory mechanism may function by shifting the ionic and/or electric concentration within the capillary lumen. The surface of hemoglobin, a basic constituent of the erythrocyte, contains charged side chains, whereas its interior is composed of neutral amino-acid side chains and hydrocarbons.

The electrically charged character of hemoglobin may impart properties to the erythrocyte, making its transit responsive to local electric fields. The initial direction Doctors Bloch and Hollander are investigating is this potential regulating mechanism.

A definitive start has been made to describe the functional units in various systems. Bloch has evaluated liver blood flow patterns and tissue structure. He has devised a scheme for its cellular and microcirculatory topology. This array outlines potential cites of liver function.

To coordinate the structural elements with specific functions, Dr. Urquhart is evaluating the hepatic responses to metabolic signals. He is measuring the glucose output response to changing pancreatic and pituitary activity levels.

The striated muscle functional unit is under study. From the analysis of latex infused corrosion specimens and specimens whose microvasculature has been filled with dyes, sectioned into sheets and evaluated with the

light microscope, the transition from an arteriole into a capillary bed is being mapped. This involves the structural overlap of adjacent terminal arteriolar segments and their parallel and serially arrayed capillary beds.

The relationship between the muscle fiber and capillary number, length and crossover paths is being evaluated. The distance between parallel capillaries appears to be dependent more upon the oxygen diffusion distance than upon a strict geometric relationship. With this as a guide, a foundation is being developed for correlating capillary and muscle fiber topology with the nerve supply (motor and autonomic) to both muscle fibers and vascular bed.

To provide a model of cardiac regulation, GTS and Urquhart have investigated the dynamic aspects of heart rate. In a paper presented at the spring 1971 FASEB meeting, by Iberall and Weinberg, a heart rate model was proposed. This model, built upon experimental findings states that the heart rate can be divided into three components. The first, the intrinsic rate, is generally cast and independent of physical status. This is inversely proportional to the $1/4$ power of body weight. The second component is the long term status component. This factor can only be changed over periods of not less than several weeks. It is the variant of athletic training. The third and most rapidly adapting component, responds to immediate bodily status changes. It is tied to transient emotional and physiologic needs.

A second paper was presented at the Biophysical Society Annual Meeting in 1971. This paper, "The weight specific nature of blood flow and oxygen uptake", by Iberall and Weinberg, developed the thesis of blood flow being proportioned to the 0.9 power of weight, not as currently related to surface area. This relationship is valid for a weight range of 10^5 gms.

Although there has been no formal meeting of all consultants within the past year, communication among the individuals has been maintained.

Bloch and Hollander are designing an experimental protocol for evaluating transcapillary potential gradients as they correlate with erythrocyte flow.

Urquhart and Bloch are working in parallel, trying to locate specific sites, involved in hepatic metabolic pathways.

GTS has met individually with all members of the consulting team and guided their work toward an efficient coordinated research effort.

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